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Case Report

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Sodium glucose co-transporter 2 inhibitors in patients with resistant hypertension: a case study

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Lesson

Sodium glucose co-transporter 2 inhibitors lower blood pressure by osmotic diuresis and can be considered in diabetic patients with resistant hypertension.

Keywords

SGLT2 inhibitor, canagliflozin, resistant hypertension, diabetes, obesity

Case presentation

A 68-year-old male patient with a medical history of long-standing hypertension, ischaemic heart disease, obesity, type 2 diabetes mellitus and rheumatoid arthritis was referred by his general practitioner to the hypertension clinic in May 2007, due to uncontrolled hypertension despite three antihypertensive agents at maximum tolerated doses (ramipril, felodipine and atenolol). His mean daytime blood pressure at the time of referral was 168/99 mmHg. He was thoroughly investigated for secondary causes of hypertension, but none were found. His antihypertensive medication regimen was progressively optimised over many years, taking into account intolerances, adverse effects and co-morbidities. His medications at the time of the addition of canagliflozin can be seen in Table 1.

In view of apparent resistance to treatment, the patient was admitted to hospital for directly observed therapy in June 2013 to exclude non-adherence. His adherence was also confirmed on two separate occasions in 2014 when urinary drug screening became routinely available. Renal denervation (radio-frequency ablation of the renal sympathetic nerves surrounding the renal arteries) was conducted in October 2013. This had no effect, and in fact his blood pressure in June 2014 was higher with a mean daytime blood pressure of 181/105 mmHg.

The patient was started on the sodium glucose co-transporter 2 inhibitor canagliflozin 100 mg in May 2015 in view of a high body mass index of 38 and suboptimal diabetes control (HbA_{1c} of 103 mmol/mol). This was uptitrated to 300 mg daily. A significant reduction in the patient's blood pressure occurred with the best clinic reading being 137/80 mmHg. The HbA_{1c} also reduced significantly (see Table 2), although this cannot be solely attributed to canagliflozin, as the doses of metformin and gliclazide were also uptitrated. The patient did not experience any unwanted effects although the creatinine measurement did increase over this time. In line with manufacturer recommendations, the dose was reduced to 100 mg in view of the estimated glomerular filtration rate dropping to less than 60 ml/min. Blood pressure recorded in clinic at the end of July 2015 was 121/68 mmHg, which was the lowest it had ever been since 2007.

At this point the canagliflozin was stopped as it was not felt necessary for his diabetes control and because of the reduction in estimated glomerular filtration rate. In the next clinic in August 2015, blood pressure measurement was again high, the lowest being 151/87 mmHg. In view of the apparent remarkable effect on the patient's blood pressure, a decision was made in conjunction with the patient to restart the canagliflozin at a low dose of 100 mg daily and cautiously monitor the kidney function. After restarting the canagliflozin 100 mg in August 2015, the blood pressure reduced to 138/86 mmHg in the next clinic. The blood pressure remained well controlled at 136/83 at the clinic visit in November 2015.

Discussion

Almost all of the glucose filtered by the glomeruli is reabsorbed, primarily in the early proximal convoluted tubule via action of sodium glucose co-transporter 2, a high-capacity, low-affinity transporter that is selectively expressed in the kidney.[1] Sodium glucose co-transporter 2 expression is increased in humans with diabetes mellitus and Zucker diabetic fatty rats, correlating with glomerular hyperfiltration and increased glucose reabsorption, as well as increased sodium reabsorption.[2] This contributes to sodium retention and hypertension in diabetic patients, the two often co-existing. There is also animal model evidence supporting a role for sodium glucose co-transporter 2-mediated sodium reabsorption in the

Table 1. Medications the patient was taking prior to the addition of canagliflozin.

Drug	Dose	Frequency	Class
Ramipril	10 mg	Once daily	Angiotensin-converting enzyme inhibitor
Diltiazem-modified release	200 mg	Once daily	Calcium channel blocker
Bisoprolol	10 mg	Once daily	Beta-blocker
Doxazosin-modified release	8 mg	Once daily	Alpha-adrenoceptor antagonist
Furosemide	40 mg	Once daily	Loop diuretic
Amiloride	25 mg	Once daily	Potassium-sparing diuretic
Gliclazide	160 mg	Twice daily	Sulphonylurea
Isosorbide mononitrate-modified release	25 mg	Once daily	Long-acting nitrate
Atorvastatin	80 mg	Once daily	HMG Co-A reductase inhibitor
Aspirin	75 mg	Once daily	Antiplatelet
Metformin	1000 mg	Twice daily	Biguanide
Methotrexate	17.5 mg	Once weekly	Antifolate disease modifying drug
Folic acid	5 mg	Once weekly	N/A
Etanercept	10 mg	Once weekly	TNF inhibitor

Table 2. Timeline of the patient's blood test results, weight and clinic blood pressure in relation to canagliflozin dose.

Clinic date	26 February 2015	8 June 2015	8 July 2015	20 July 15	6 August 2015	20 August 2015	1 October 2015	12 November 2015
HbA_{1c}, mmol/mol	103	61		40			49	
Best clinic BP, mmHg	177/99	137/80		121/68	151/87	138/86	147/85	136/83
Sodium, mmol/L	135	142		142	141	142	141	137
Potassium, mmol/L	4.1	4.3		4.1	4.4	4.1	4.2	4.8
Urea, mmol/L	6.0	6.0		6.5	4.9	6.1	5.7	7.9
Creatinine, μmol/L	97	107		120	105	105	96	114
eGFR, ml/min	67	60		52	61	61	68	56
Weight, kg	119	113.9		113.9			113.1	112.7
Canagliflozin, daily dose	100 mg started May 2015	Increased to 300 mg	Reduced to 100 mg	Stopped	Restarted 100 mg	100 mg	100 mg	100 mg

development of hypertension: in hypertensive rats, angiotensin II has been shown to regulate the increase in sodium glucose co-transporter 2 expression via the angiotensin II AT1 receptor.[3]

Canagliflozin and dapagliflozin were two of the first sodium glucose co-transporter 2 inhibitors to be approved in Europe and the United States for use in diabetic patients, and others soon followed.

Our experience with the patient in this case study is expected to be a class effect, not specific to canagliflozin. Clinical trials with these agents have consistently shown beneficial effects not only on diabetes control but also on blood pressure and weight. They have been shown to produce a reduction in HbA_{1c} of around 0.9%, a mean reduction in weight of 2.5 kg, a drop in systolic blood pressure of 4 mmHg and a drop in diastolic blood pressure of 1.6 mmHg.[4–6] In the recently published EMPA-REG study, it has been shown that the sodium glucose co-transporter 2 inhibitor empagliflozin reduces cardiovascular mortality by 38% and all-cause mortality by 32%, in high cardiac risk type 2 diabetes mellitus patients.[5] It has also been shown to reduce heart failure mortality by 35% and this been attributed, in part, to effects on blood pressure, amongst other things.[7]

Sodium glucose co-transporter 2 inhibitors have been postulated to reduce blood pressure via their osmotic diuretic action.[1] They work on a different site to loop diuretics and thiazides, which act on the thick ascending limb of the loop of Henlé and the distal convoluted tubule, respectively. Caution is advised when used in combination with loop diuretics such as furosemide due to risk of hypovolaemia, although concomitant use is not contra-indicated.

Typical characteristics of patients with resistant hypertension include co-morbidities such as obesity and type 2 diabetes, as well as obstructive sleep apnoea, older age, target organ damage and atherosclerotic vascular disease.[8] It could be argued that sodium glucose co-transporter 2 inhibitors can play a role in the management of such patients not only for their diabetes but also for their high blood pressure and obesity. However, such medications should be used under close supervision in patients with chronic kidney disease and in those taking a combination of diuretics.

Declarations

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Guarantor: AO

Contributorship: All authors contributed equally.

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